In re Appln. of HISADA et al.
Application No. 09/622,206

REMARKS

The Pending Claims

Claims 1, 3-5, and 8 are currently pending and directed to a method for quantitatively detecting an antigen.

Amendments to the Specification and Claims

The specification has been amended to remove obvious typographical, idiomatic or grammatical errors. Claim 1 has been amended to include the limitation of claim 2 and to recite that the detected fluorescence is correlated with the amount of antigen. The amended claim is supported by the original claims and the specification. The specification as a whole supports the concept of correlating the detected fluorescence with the amount of antigen, as would be understood by those skilled in the art; see, for example, page 2, line 25 to page 3, line 10. No new matter has been added by way of these amendments.

Summary of the Office Action

The Office has objected to the specification for alleged informalities. Claims 1-5 and 8 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Additionally, claims 1-5 and 8 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent 5,348,633 (Karger et al.) in view of U.S. Patent 5,630,924 (Fuchs et al.) and Chen et al., *Electrophoresis, 15(1),* 13-21 (1994). The Office has rejected claims 2 and 8 under 35 U.S.C. § 103(a) as allegedly unpatentable over Karger et al., Fuchs et al., and Chen et al., and further in view of WO 89/01974 (Bodmer et al.) and U.S. Patent 4,816,567 (Cabilly et al.). Reconsideration of these rejections is hereby requested.

Discussion of the Objection to the Specification

The Office has objected to the specification for alleged informalities. Applicants have amended the specification as discussed above. In view of the foregoing, as well as the amendments made to the specification in response to the previous Office Action and the Preliminary Amendment, applicants respectfully request that the objection to the specification should be withdrawn.

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Discussion of the Indefiniteness Rejection

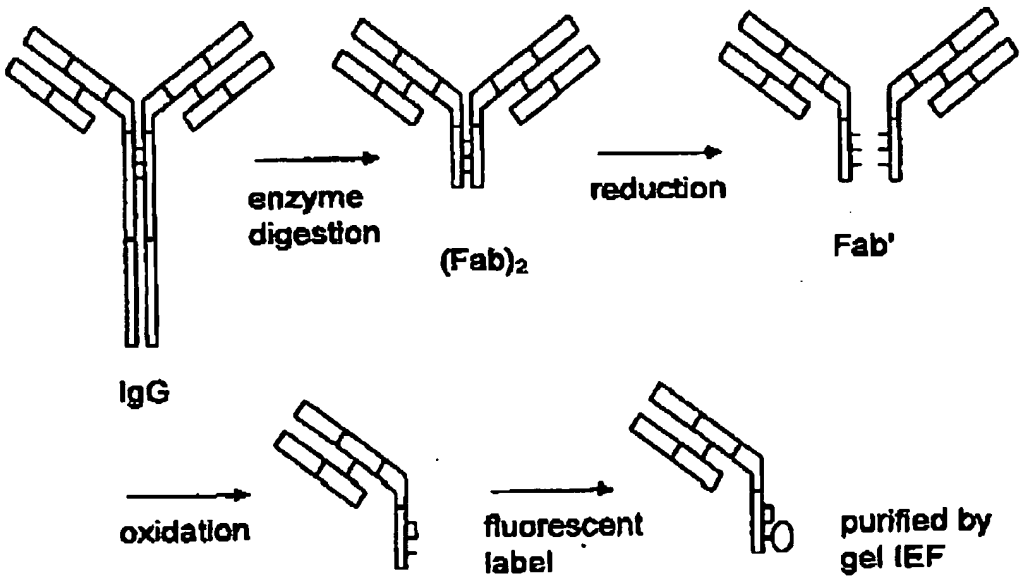
The Office has rejected claims 1-5 and 8 as allegedly indefinite. Applicants have amended claim 1 to recite that the detected fluorescence is correlated with the amount of antigen. Accordingly, the rejection should be withdrawn.

Discussion of the Obviousness Rejections

The Office has rejected claims 1-5 and 8 as allegedly obvious over the combination of several references. These rejections are traversed for the following reasons. In addition, claim 1 has been amended as discussed above.

The present invention involves the use of a Fab' antibody to detect an antigen by electrophoresis, wherein the Fab' antibody is fluorescently-labeled and having a uniform isoelectric point (pI). The value of pI is varied retaining these two features (fluorescent label and uniform pI). The antibody has been modified by the amino acid sequence and the fluorescent label.

Karger et al. does not modify the antibody by an amino acid sequence. Rather, Karger et al. goes through a number of steps to prepare an antibody labeled at a single sulfhydryl group at the hinge region, as illustrated below.



The Office contends that Fuchs et al. teaches that it was well known in the art that the electrophoretic mobility of a labeled antibody in capillary electrophoretic methods could be altered by attaching charged groups to the labeled antibody, and relies on col. 2 of Fuchs et al. The Office also contends that Fuchs et al. teaches methods of labeling and charge modification of monoclonal antibody fragments, for example, by the addition of charged amino acid sequences. The Office relies on col. 11-12 of Fuchs et al.

Applicants respectfully submit that Fuchs et al. teaches away from the presently claimed invention. At col. 2, lines 9-34, Fuchs et al. teaches that tailoring the electrophoretic mobility of a labeled antibody by attaching charged groups to the same labeled antibody molecule is not desirable. Fuchs et al. further teaches that such tailoring (where label and charged groups are on the same molecule) is not ideal because the ultimate objective of the assay is to separate the two labeled species formed in a typical binding assay (labeled antibody-antigen complex and unbound labeled antibody). Fuchs et al. further teaches that under the above discussed tailoring, both such species will be influenced by the charge tailoring and result in undermining efforts to differentiate between labeled species. Accordingly, Fuchs et al. teaches the use of two partners - the first binding partner having a label and the second binding partner having a charge modification. At col. 11, lines 5-52, Fuchs et al. teaches charge-modifying the second binding partner. At col. 12, lines 18-20, Fuchs et al. states that detectable or charge-modifying moieties can be attached to the above-described antibody fragments. That is, Fuchs et al. teaches that either a detectable moiety (label) or a charge-modifying moiety should be attached to the antibody but not both moieties to the same molecule.

In view of the foregoing, there is no motivation for one of ordinary skill in the art to modify the same antibody fragment to incorporate both label and charge-modifying group on the same molecule, especially in view of Fuchs et al.'s teaching that such tailoring (to have both modifications on the same antibody molecule) is undesirable.

To establish a *prima facie* case for obviousness, there are two criteria: (1) the cited references must suggest the desirability of the proposed modification; see, e.g., *In re Laskowski*, 871 F.2d 115, 117, 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) ("the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification") and (2) there must be a reasonable expectation of success.

Here, the proposed modification has been clearly taught as undesirable. Thus, the first prong of the test for establishing a *prima facie* case for obviousness has not been

satisfied by the Office. Accordingly, the rejection is erroneous and should be withdrawn. Further, the second prong of the test also is not satisfied. There is no reasonable expectation of success. Expectation of success must be determined from the vantage point of the skilled artisan at the time the invention was made. In other words, hindsight analysis is not allowed. *See, Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Those of ordinary skill in the art reading Fuchs et al. as well as Chen et al. at the time the presently claimed invention was made, would not expect that tailoring the same molecule would have a reasonable chance of success. Further, when labeling the amino acid residues of the amino acid sequence with fluorescent dyes, since the dye will be linked to the amino groups (and there are many of these), it would be difficult to control the position and number of the linked fluorescent dye molecules, consequently leading to heterogeneity in the isoelectric point (pI) of the fluorescently-labeled amino acid sequence. Therefore, the obviousness rejection involving a combination of Karger et al. and Fuchs et al. is erroneous and should be withdrawn.

Further, none of the cited references, either alone or in combination, suggests to those of ordinary skill in the art the presently claimed invention wherein the charge-modifying moiety is linked to the C terminus of the light chain. The position where the detectable moiety and/or charge-modifying moiety is linked to the Fab' antibody is the single sulfhydryl group in the hinge region in Karger et al., Fuchs et al., and Chen et al. Particularly, in Chen et al., the detectable moiety is linked at one end of charge-modifying moiety (synthetic oligonucleotides) and the antibody is linked via single sulfhydryl group in the hinge region at the other end of the charge-modifying moiety.

Bodmer et al. and Cabilly et al. fail to cure the deficiencies of Karger et al., Fuchs et al., and Chen et al. One of ordinary skill in the art would not have been motivated to modify the disclosures of Karger et al., Fuchs et al., Chen et al., and/or Bodmer et al., based on the teachings of Cabilly et al. to arrive at the present invention.

In addition, the method of the present invention leads to the production of an Fab' fragment without amino acids that cause the nonuniformity of isoelectric points (i.e., an Fab' fragment with a uniform isoelectric point). For the above reasons, the method of quantitatively detecting an antigen recited in the pending claims is not obvious to those of ordinary skill in the art, and the rejections should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance. Alternatively, the amendments and remarks place the application in better condition for consideration on

appeal. Accordingly, the Examiner is respectfully requested to enter the amendments. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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